

## Evidence-based Practice Center Systematic Review Protocol

### Project Title: Screening for Hepatitis C

## I. Background and Objectives

### Objective

The stated objective of our systematic review is to evaluate the existing literature on screening for hepatitis C virus (HCV) infection.

### Summary of Nomination

This topic was nominated by an organization interested in updating a recommendation on screening for HCV infection.<sup>1,2</sup> In 2004, the U.S. Preventive Services Task Force found insufficient evidence to recommend for or against routine screening for HCV infection in adults at high risk for infection. The systematic review that supported this recommendation also evaluated the effectiveness of treatment for HCV infection within the context of screening and risk assessment of the general population.<sup>1,2</sup> Another organization was also interested in factors that predict treatment response in relation to outcomes, such as adherence to treatment. During discussions with Key Informants, our interest in expanding the scope of HCV treatments arose. Therefore, three separate but complementary reviews will be conducted and will focus respectively on HCV screening, HCV treatment, and adherence to HCV antiviral therapy. This protocol will address HCV screening in a general population, the topic that was originally nominated.

### Background and Clinical Context

HCV is the most common blood-borne pathogen in the United States; infection with HCV is usually chronic. The virus is primarily transmitted through percutaneous exposure to blood, with the most common risk factors being intravenous drug use, multiple sexual partners, and sexual contact with an HCV-infected person. The prevalence of HCV infection in the United States is estimated to be 1.6 percent, with a peak of 4.3 percent in people 40 to 49 years of age.<sup>3</sup> Approximately 78 percent of people who test positive for anti-HCV antibody have chronic HCV infection.<sup>3</sup> The Centers for Disease Control and Prevention (CDC) estimates that there were 17,000 new cases of HCV infection in 2007.<sup>4</sup> Infection with HCV is a leading cause of chronic liver disease in the United States, with the direct medical costs of HCV-related liver disease projected to reach \$10.7 billion by the year 2019.<sup>5</sup> The CDC estimates that 60 to 70 percent of HCV-infected adults are asymptomatic.

## II. Key Questions and Population, Intervention, Comparator(s), Outcome(s), Timing and Setting(s) [PICOTS]

### Key Questions

The Key Questions (KQs) were revised according to comments received during their public posting and based on input from the Technical Expert Panel (TEP). The changes we made are summarized below:

- Clarity:
  - KQ 1a: “asymptomatic” to “asymptomatic adults without known abnormal liver function tests”
  - KQ 4b: “qualify” to “receive”
  - KQ 6: “counseling *and* immunizations” to “counseling *or* immunizations”
- Include additional outcome measures for KQ 4b, specifically the number needed to screen for HCV infection and the proportion of HCV infections identified and missed with different screening strategies
- Include incidence of HCV infection as a clinical outcome (incorporates transmission)

### Question 1

This KQ has two parts:

- a. Does screening for HCV infection in nonpregnant adults without known abnormal liver function tests reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?
- b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?

### Question 2

This Key Question has two parts:

- a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?
- b. What is the sensitivity and number needed to screen of different risk- or prevalence-based methods for screening for HCV infection?

### Question 3

What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?

### Question 4

This KQ has two parts:

- a. What is the comparative effectiveness of various tests and strategies for the workup to guide treatment decisions in patients who are HCV positive?
- b. What proportion of patients with screen-detected HCV infection receives treatment?

### Question 5

What are the harms associated with the workup for guiding treatment decisions?

### Question 6

This KQ has three parts:

- a. How effective is counseling or immunizations of patients with HCV infection at improving health outcomes or reducing the spread of HCV?
- b. Does becoming aware of positive HCV infection status decrease high-risk behaviors?
- c. How effective is counseling or immunizations of patients with HCV infection at improving intermediate outcomes, including change in high-risk behaviors?

### Question 7

Do any interventions decrease or increase the vertical transmission of HCV during delivery or in the perinatal period?

### PICOTS Criteria

With input from Key Informants, the Agency for Healthcare Research and Quality (AHRQ), and the TEP and based on comments from public posting of the KQs, we decided to exclude the following from our review:

- Fibroscan<sup>®</sup> and breath tests will not be evaluated because they are not approved by the U.S. Food and Drug Administration nor are they widely used in clinical practice in the United States.
- Child outcomes related to screening during pregnancy will not be evaluated because they are outside the scope of this review and are to be nominated as a separate review.

### Population:

1. Asymptomatic adults

- a. Includes individuals without signs or symptoms suggestive of liver disease or known abnormal liver function tests
  - b. Excludes people who are HIV positive, transplant recipients, and patients with renal failure
2. Asymptomatic pregnant women
  - a. Includes women without signs or symptoms suggestive of liver disease
  - b. Excludes people who are HIV positive, transplant recipients, and patients with renal failure
3. Targeted population of asymptomatic patients at higher risk for HCV infection, based on clinical or demographic characteristics, such as:
  - a. Intravenous drug use
  - b. High-risk sexual behaviors
  - c. Age group(s) with high prevalence of HCV infection

#### **Interventions:**

1. Screening for HCV (KQs 1a, 1b, 2a, 2b, and 3)
  - a. HCV antibody test
  - b. Confirmatory HCV RNA testing as indicated
2. Noninvasive screening approaches for the workup to guide treatment decisions (KQs 4a, 4b, and 5)
  - a. Blood tests
  - b. Imaging techniques
3. Counseling against risky behaviors and alcohol use (KQs 6a and 6c)
4. Immunizations for hepatitis A virus or hepatitis B virus (KQs 6a and 6c)
5. Nondrug interventions (e.g., labor and delivery interventions) that may decrease or increase vertical transmission of HCV (KQ 7)

#### **Comparators:**

1. No screening for HCV (KQs 1a, 1b, and 3)
2. Screening of the general population versus “targeted” high-risk groups (KQ 2)
3. Standard workup including liver biopsy (KQs 4a, 4b, and 5)
4. No counseling (KQs 6a and 6c)
5. No immunization for hepatitis A virus or hepatitis B virus (KQs 6a and 6c)
6. No intervention (KQ 7)

#### **Outcomes:**

**Source:** [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)

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1. Intermediate outcomes

- a. Number needed to screen; proportion of HCV infections identified and missed (KQ 2b)
- b. Measures of diagnostic accuracy, such as sensitivity, specificity, predictive values, and areas under the receiver operating curve (KQ 4a)
- c. Sustained virological response, liver function, and histological changes (KQ 6c)
- d. Behavioral changes associated with improved health outcomes and reduction in rates of HCV transmission (KQ 6b and 6c)

2. Ultimate health outcomes (KQs 1a, 1b, 2a, 4a, 6a, and 7)

- a. Mortality due to HCV infection
- b. Morbidity due to HCV infection including hepatic cirrhosis, hepatocellular carcinoma, and liver transplants
- c. Incidence of HCV, including vertical transmission
- d. Quality of life

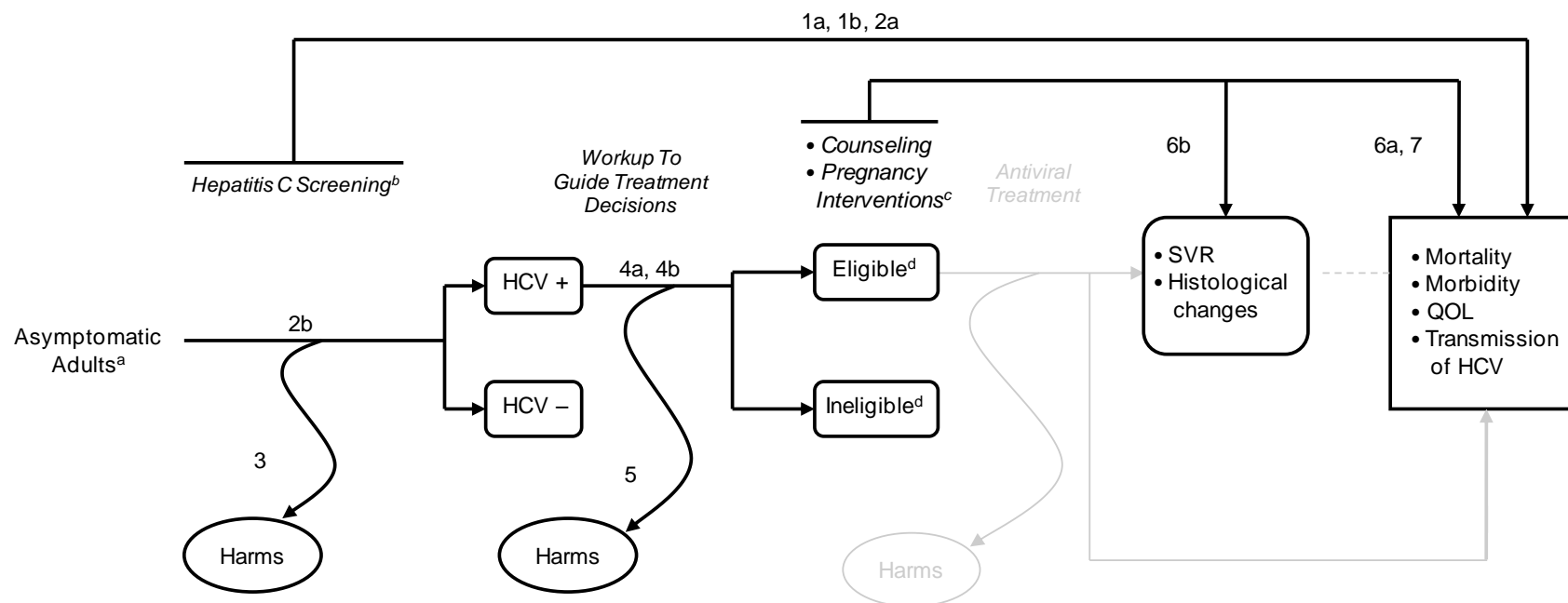
3. Adverse effects of intervention(s) (KQ 3)

4. Harms from screening and/or workup to guide treatment decisions (KQ 5)

**Timing and Setting:**

No minimum time period required, and all settings included.

### III. Analytic Framework: Screening for HCV



- <sup>a</sup> Nonpregnant and pregnant adults without abnormal lab values. Excluding people with HIV, transplant recipients, and patients with renal failure.
- <sup>b</sup> HCV antibody testing with confirmatory HCV RNA testing as indicated.
- <sup>c</sup> Interventions that may affect vertical transmission of HCV, such as caesarian section, amniocentesis, fetal monitoring, or others.
- <sup>d</sup> Refers to eligibility for antiviral treatment based on viral and host factors.

Abbreviations: HCV = hepatitis C virus; QOL = quality of life; SVR = sustained virological response

## IV. Methods

### A. Criteria for Inclusion/Exclusion of Studies in the Review

Literature to be included will meet the PICOTS criteria outlined above. We will include observational studies, systematic reviews, and clinical trials. We will exclude case studies and small case series. Non–English-language articles will be included in this review and translated when it is feasible to do so.

### B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

Results from previously conducted meta-analyses and systematic reviews on these topics will be sought and used where appropriate and updated when necessary. In addition to using MEDLINE® to identify systematic reviews, we will search the Cochrane Databases of Systematic Reviews and Controlled Trials and Database of Abstracts of Reviews of Effectiveness.

To identify articles relevant to each KQ, a research librarian will search the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, Evidence-Based Medicine Reviews (EBMR) and Ovid MEDLINE® (see Table 1 for a sample search strategy). Grey literature will be identified by searching clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, Clinical Trial Results, WHO Trial Registries), grants databases (NIH RePORTER, HSRProj, AHRQ GOLD), and the Web sites of individual funders.

Abstracts and full-text articles will be reviewed in duplicate for inclusion and exclusion for each KQ. After finalizing literature searches, the research team will review titles and abstracts using our pre-established inclusion/exclusion criteria to determine potential eligibility for inclusion in the evidence synthesis. All citations that are judged to meet the inclusion criteria by at least one reviewer will be retrieved for full-text review.

All retrieved studies will be reviewed in duplicate. Data will be extracted from studies that meet our inclusion criteria and entered into an electronic database. A consensus process will be used to arbitrate conflicting assignments eligibility and ineligibility, and a file of excluded studies with reasons for the exclusion of each will be maintained. Searches will be updated while the report is posted for public comment and peer review to capture new publications. Literature identified during the updated search will go through the same process of dual review as all other studies considered for inclusion in the report. If any pertinent new literature is identified for inclusion in the report, it will be incorporated before the report is finalized.

**Table 1. Sample search strategy**

	Concept	Search String	N
1	Hepatitis C	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus\$.mp. or HCV.mp	51314
2	Screening	Mass screening/ OR population surveillance/ OR sentinel Surveillance/ OR ((public\$ or communit\$ or universal\$ or widespread or open\$ or unrestricted or group\$ or adult\$) adj3 (screen\$ OR test\$ or surveillance)).mp OR (antibod\$ ADJ3	184701

	(test\$ or screen\$ or surveillance)).mp OR Seroepidemiologic Studies/	
	1 AND 2	3711
	Limit: adult (19-44), Middle Age (45-64), All Aged (65+) and publication date = 2002-current humans NOT animals	<b>840</b>

### C. Data Abstraction and Data Management

Data abstractions will be completed by one investigator, and a second investigator will review each abstraction for accuracy. The following data will be extracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, and diagnosis) eligibility and exclusion criteria, hepatitis C intervention and comparisons, the method of outcome ascertainment if available, and results for each outcome. We will record intention-to-treat results if available.

### D. Assessment of Methodological Risk of Bias of Individual Studies

We will assess the risk of bias of systematic reviews, randomized trials, and cohort and case control studies based on predefined criteria. We will adapt criteria from the Assessment of Multiple Systematic Reviews (AMSTAR) tool (systematic reviews), methods proposed by Downs and Black (observational studies)<sup>6</sup>, and methods developed by the U.S. Preventive Services Task Force.<sup>7</sup> Results from high risk of bias studies will most likely be excluded from data syntheses, though these data will still be included in evidence tables. The criteria we will use are consistent with the approach recommended by AHRQ in the prepublication draft of the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter *Methods Guide*).<sup>8</sup>

### Systematic Reviews

Included systematic reviews will also be rated for risk of bias based on predefined criteria, assessing whether they had a clear statement of the research questions(s), reported inclusion criteria, used an adequate search strategy, assessed validity, reported adequate detail of included studies, and used appropriate methods to synthesize the evidence. We will include systematic reviews and meta-analyses that included unpublished data inaccessible to the public, but because the results of such analyses are not verifiable, we will consider this a methodological shortcoming.

### Trials

We will rate the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories will be rated as having a high risk of bias; trials that met all criteria will be rated as having a low risk of bias; the remainder will be rated as having a



moderate risk of bias. As the “moderate risk of bias” category is broad, studies with this rating vary in their strengths and weaknesses: the results of some moderate risk of bias studies are *likely* to be valid, while others are only *probably* valid. A “high risk of bias” trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared interventions.

## Observational Studies

For assessing the internal validity of observational studies, we will evaluate whether they used nonbiased selection methods; whether rates of loss to followup were acceptable; whether predefined outcomes were specified; whether they used appropriate methods for ascertaining exposures, potential confounders, and outcomes; and whether they performed appropriate statistical analyses of potential confounders. Although many tools exist for quality assessment of nonrandomized trials, there is no consensus on optimal rating methods (9). We therefore will not use a formal scoring system to rate the risk of bias in observational studies included in our review but will note methodological deficiencies in any of the above areas when present.

### E. Data Synthesis

We will construct evidence tables showing study characteristics and risk-of-bias ratings for all included studies. To determine the appropriateness of meta-analysis, we will consider the clinical and methodological diversity and assessed statistical heterogeneity. Appropriate measures will be chosen based on the type of data for meta-analysis. We will use standard  $\chi^2$  tests to assess the presence of statistical heterogeneity among studies and the  $I^2$  statistic to test the magnitude of heterogeneity. When appropriate, we will use a random effects model to combine studies while accounting for variation among studies. We will use a fixed effects model to combine rare binary outcomes. When there is no variation among studies, the random effects model yields the same results as a fixed effects model. Statistical heterogeneity will be explored by using subgroup analysis or meta-regression.

When statistical meta-analysis is not possible, we will group studies by similarity of intervention characteristics and plot trends in the study findings. Where possible, we will group similar outcome measures across the studies to make preliminary estimates of effect sizes. Direct comparisons will be made when head-to-head trials are available. Otherwise, indirect comparisons will be considered if the outcome measures for nonintervention are similar across the studies evaluated.

### F. Grading the Evidence for Each Key Question

We will use the methods outlined in Chapter 10 of the AHRQ *Methods Guide*<sup>8</sup> to grade strength of evidence. (An edited version of the chapter has also been published in the *Journal of Clinical Epidemiology*.<sup>10</sup>)

### G. Applicability

This review is not applicable to patients with signs or symptoms of liver abnormalities, transplant recipients, or patients who are coinfectd with HIV. We will assess the applicability of studies in terms of the degree to which the study population, interventions, outcomes, and settings are relevant to individuals who would be considered for HCV screening and features that may affect the effectiveness of an HCV intervention.

## V. Definition of Terms

Not applicable.

## VI. References

1. Chou R, Clark EC, Helfand M, for the US Preventive Services Task Force. Screening for hepatitis C virus infection: a review of the evidence for the US Preventive Services Task Force. *Ann Intern Med* 2004;140(6):465-79. PMID: 15023713.
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4. Centers for Disease Control and Prevention. The ABCs of hepatitis. Atlanta, GA: US Department of Health and Human Services; June 2010. Publication No. 21-1076. Available at: <http://www.cdc.gov/hepatitis/Resources/Professionals/PDFs/ABCTable.pdf>. Accessed November 10, 2010.
5. Wong JB, McQuillan GM, McHutchison JG, et al. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* 2000;90(10):1562-9. PMID: 11029989.
6. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies in health care intervention. *J Epidemiol Community Health* 1998;52(6):377-84. PMID: 9764259.
7. Harris RP, Helfand M, Woolf SH, et al, for the Methods Work Group of the Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20(3 Suppl):21-35. PMID: 11306229.
8. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2011. Chapters available at: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov).
9. Deeks JJ, Dinnes J, D'Amico R, et al, for International Stroke Trial Collaborative Group and the European Carotid Surgery Trial Collaborative Group. Evaluating non-randomized intervention studies. *Health Technol Assess* 2003;7(27):iii-x, 1-173. PMID: 14499048.
10. Owens DK, Lohr KN, Atkins D et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. *J Clin Epidemiol* 2010;63(5):513-23. PMID: 19595577.

## Amendments

Not applicable at this time.

## VIII. Review of Key Questions

For all EPC reviews, key questions are reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions are posted for public comment and finalized by the EPC after review of the comments.

## IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **X. Technical Expert Panel (TEP)**

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **XI. Peer Review**

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.